

Clues from a chemical

PCPA's effects on the brain amine serotonin are stimulating new research

by Louise Campbell

"We must hurry," Sigmund Freud once said to his colleagues, gathered for their weekly meeting in his Vienna flat above a grocery store. "The men with the hypodermic syringes are on our heels."

Freud believed that science would someday demonstrate the biochemistry of mental illness. But listening to neurotic women painfully recall forgotten sexual wishes—recollections that sometimes removed such hysteric symptoms as paralysis of an arm or failure of vision—Freud came to believe that conflicts about the deep instinctual drive of sex caused much mental illness. He also found that by describing their dreams, patients could bring back feelings of rage and shame associated with the repressed sexual wishes. Experiencing these feelings seemed to aid recovery.

The chemistry of the brain is still a mystery. But the profession of psychiatry has continued to build on the triad the Viennese explorer first linked—sex, dreams and mental illness. Perhaps no medical hypothesis has aroused more controversy than Freud's view that derangement of the sexual drive is the basic cause of neurosis.

This view, like most of the diverse psychiatric explanations that have followed it, was based on observation. Psychiatrists do not have an experimental method. Many have hoped that the current brisk study of brain biochemistry would bring psychiatry closer to an exact science.

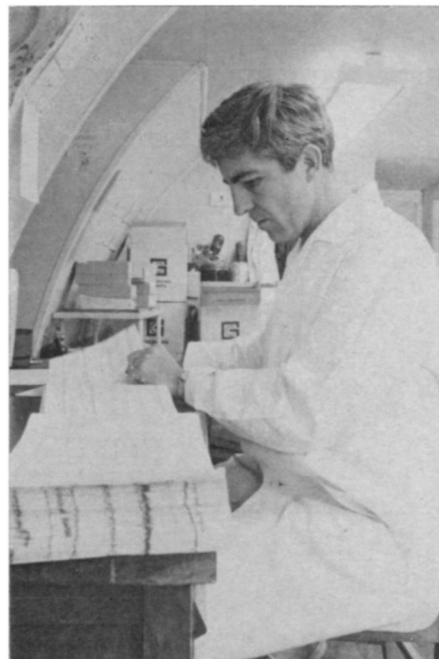
In this perspective, laboratory study of an experimental drug's effects on the sexual behavior of certain animals is arousing interest among investigators in many fields. The drug also produces

insomnia in some animals and changes the part of sleep—rapid-eye-movement (REM) sleep—that workers in this field think is associated with dreaming in both humans and animals. (Even birds have fleeting moments of REM sleep.) And, in one of its most puzzling effects, the drug evokes intense rage in some cats, affection in others.

The drug, para-chlorophenylalanine (PCPA), is not new, but its effect on the animal brain was discovered only a few years ago by Drs. B. K. Koe and Albert Weissman of the Pfizer Research Laboratories in Groton, Conn. These researchers reported that the drug sharply reduces the level of a naturally occurring neurochemical, serotonin, in the brain of rats, mice and dogs. They noticed no effect on the behavior of the animals and said that their ability to perform simple experimental tasks to get food rewards was unimpaired. Other workers soon confirmed the serotonin suppression, and began to find some behavioral effects. Rats, for instance, showed an aversion to alcohol after taking the drug (SN: 7/13/68, p. 37).

Serotonin (5-hydroxytryptamine), first found in human blood by Dr. Irvine Page and workers at the Cleveland Clinic, is now known to be secreted by the pineal gland (once a third eye on the way to mammalian evolution) and to be present in many parts of the human nervous system. It is also found in the venom of wasps and cobras and is one of the compounds whose oxidation makes bananas turn brown.

Little is known about how serotonin acts in the brain, and investigators quickly recognized that PCPA could be used to study this brain chemical. PCPA is the first experimental drug that makes

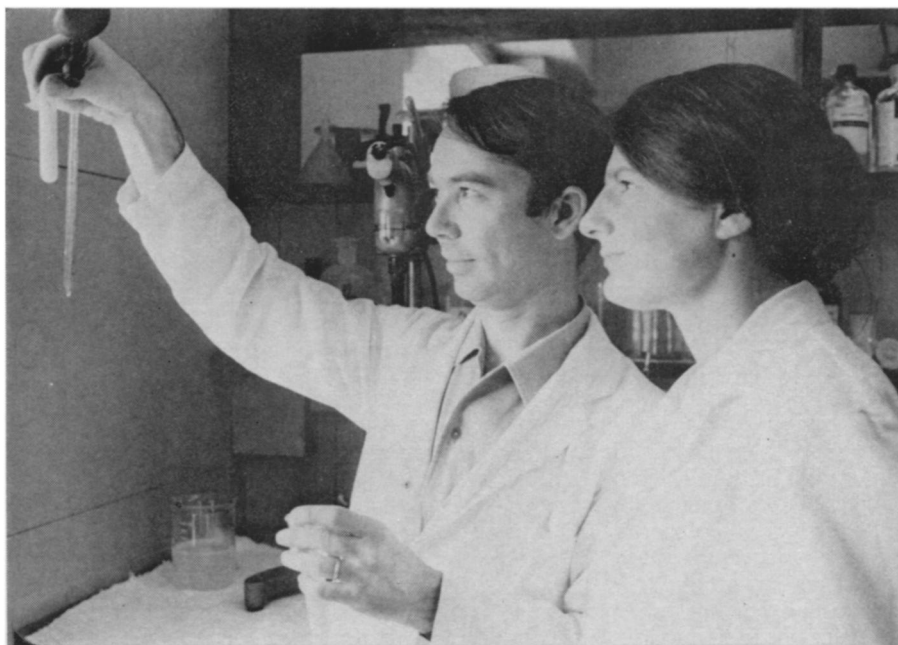


Stanford Univ.

Dement looks for dream mechanisms.

it possible to separate the effect of serotonin from the effects of two other known brain amines (compounds that carry nitrogen on their carbon rings).

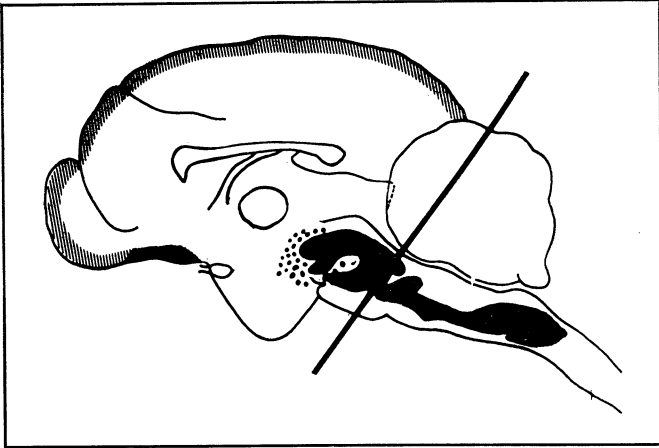
Other compounds are known that reduce brain serotonin—reserpine, one of the first-discovered tranquilizers, is an example—but these also reduce the levels of two other important brain amines—norepinephrine and dopamine. Thus these nonselective depressors were not much help to researchers seeking to learn something about how each of these three brain amines act. (Other neurochemicals are known to be present in the human brain—acetylcholine, transmitter of the peripheral



Star Studios

Tagliamontes hope drug may help psychiatrists relieve sexual disability.

... PCPA



Jouvet

Center in cat's brain (right) produces sleep.



Stanford Univ.

PCPA produces hyperactive sexual behavior in rats.

parasympathetic nervous system is one—but ways to examine them are even less developed.)

The three brain amines are synthesized in body biochemistry from essential amino acids. PCPA reduces brain serotonin by linking to and blocking a key enzyme necessary in the synthesis of serotonin. The enzyme blockage is not reversible, but in 7 to 10 days the body regenerates the enzyme.

Sleep researchers were especially interested in PCPA. They already had some experimental evidence that serotonin is necessary to sleep and they quickly devised experiments to see if PCPA, by reducing brain serotonin, would also produce insomnia. They found that it did. And they confirmed the effect of serotonin reduction by showing that sleep could be restored by giving a serotonin precursor. The precursor, 5-hydroxytryptophan, crosses the blood-brain barrier (serotonin does not) and in one chemical step is converted to serotonin in brain cells.

A French sleep researcher, Dr. Michel Jouvet, chairman of the department of experimental medicine at the University of Lyons, showed that PCPA produces sleeplessness in cats. As a result of his earlier work, Dr. Jouvet was able to trace the PCPA effect on sleep to particular nuclei in the midline of the brain. By precise surgical removal of these midline nuclei (the raphe nuclei), Dr. Jouvet had earlier produced cats that never sleep. He then used a fluorescent technique invented by Swedish researchers to show that serotonin is present in high levels in the cells of these nuclei. (Formaldehyde makes brain amines fluorescent, and norepinephrine, dopamine and serotonin each show a different fluorescent color and spectrum.) Dr. Jouvet used the same technique to demonstrate that PCPA removes serotonin from these specific brain nuclei.

Dr. Jouvet, and Dr. William Dement

of Stanford University, are particularly interested in the effect of PCPA on REM sleep. Both have studied rapid-eye-movement sleep for more than a decade by recording the electrical activity of the eyes and various parts of the brain.

Both believe that while their work has shown serotonin to be the chemical agent of the "deep wave" sleep not accompanied by dreaming, other biochemical agents of the sleep associated with dreaming have yet to be found.

Neither worker has experimented with PCPA on humans as yet. Dr. Karl Engelman of the National Heart and Lung Institute, who has been using PCPA to reduce intestinal diarrhea in some cancer patients, did observe some effects of the drug on sleep. His patients did not become insomniac, he reports, but they no longer had REM sleep—the sleep associated with dreaming.

Although these effects on humans were different from the effects noted by Drs. Jouvet and Dement in cats, the discrepancy, at the present pioneering state of the investigation, is neither surprising nor particularly disquieting to the researchers. One reason so little is known about brain biochemistry is that human brains, with fully developed cerebral cortexes, differ markedly in function from those of any lower mammals. And each of the experimental mammalian species used differs from others in both brain anatomy and brain function.

Dr. Jouvet suggests that there are three keys to dreaming—serotonin, norepinephrine and acetylcholine—each acting on a different brain center in a given sequence.

"It is like a fail-safe system," Dr. Jouvet says, "that prevents intrusion into [the] waking [state] of the hallucinatory processes involved in dreaming." Dr. Dement, who also practices psychiatry, has suggested that in schizo-

phrenia the normal "fail-safe" system has broken down.

The sleep researchers also noticed that PCPA produces extreme sexual excitement and compulsive sexual behavior in mice, rats, rabbits and cats. Popular folklore has looked for this sort of effect in compounds ranging from the mandrake root to absinthe. When news of the aphrodisiac effect of PCPA in animals came to public attention about 10 months ago, a scientific controversy erupted.

Administrative officers at Pfizer, for example, show little enthusiasm for this possible effect. They have given the company's public relations department the job of trying to persuade reporters not to write about the sexual-excitant effect of the drug. Pfizer officials say they fear amateurs may try to make PCPA, as they have made LSD (lysergic acid diethylamide), an amine with powerful and dangerous effects on the human brain.

A group of Italian researchers now working at the National Heart and Lung Institute—including Drs. Gian L. Gessa and Alessandro and Paola Tagliamonte—believes that this experimental compound has an important future in treating human sexual disabilities. They plan to begin work with humans when they return to their own university in Sardinia at the end of this year. But clinicians who have used the drug (it is available only for experimental use in relieving diarrhea in patients who have a rare intestinal cancer, and in treating schizophrenia, for which it has not been useful) say they have not found the slightest indication that PCPA acts as a sexual stimulant in humans, and believe there is no possibility of such development.

The Italian researchers, who have been experimenting with PCPA in the National Heart and Lung Institute laboratory of Dr. Bernard Brodie, one of the pioneers in the study of brain sero-

tonin, found that PCPA induces long-lasting sexual excitation in rats and even causes rabbits, normally fearful animals, to attempt sexual behavior with cats.

At an August meeting of the American Society for Pharmacology and Experimental Therapeutics at Stanford University, Dr. Gessa reported that the male hormone, testosterone, increases the sex-stimulant effect of PCPA, causing even castrated rats to mount other rats.

"Relief of sexual disability is a moral and vital issue," Dr. Gessa said. Dr. Alessandro Tagliamonte adds: "We think psychiatrists may ultimately be able to use PCPA to relieve impotence or frigidity. We favor the Freudian view of the emotional cause of sexual disability. But we think the drug may have an adjunctive effect by producing successful behavior."

One of the factors in the controversy over whether PCPA could have sexual stimulating effects in humans may be the dosages involved.

Dr. Engelman for instance, has not seen any increase in libido in any of the patients his group treated, even though, he says, "we've questioned them carefully." But high dosages of PCPA are needed to evoke sexual excitation in rats, more than twice as high in relation to body weight as dosages of PCPA given clinically to check cancer-caused diarrhea. Such dosages would be highly toxic.

Dr. Gessa hopes that toxicity may be reduced by producing the L (levorotary) form of PCPA. This was the case with L-dopa, the drug now being used to treat Parkinson's disease. Only levorotary amino acids act in body biochemistry. It is probable that compounds derived from them, such as PCPA, should also be levorotary. Such compounds are expensive to produce synthetically.

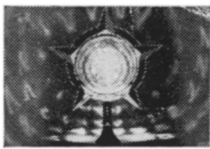
Dr. Dement and his colleagues in Stanford's Department of Psychiatry have examined the effect of PCPA in cats. They find that it not only produces insomnia and sexual excitation—all the cats in the experimental group showed hypersexuality—but other behavior that in part varies according to the disposition of individual cats. The most marked effect is rage.

"Most animals became much more vicious when subjected to PCPA treatment," says Dr. James Ferguson of the Dement group. "Several cats attacked and severely mauled experienced technicians—not to mention other cats—entirely without provocation. But a few unpredictably became more affectionate and would even prefer rubbing against the observer's legs to eating tuna fish." □

october 3, 1970

KEEP PACE WITH SPACE AGE! SEE MOON SHOTS—LANDINGS, SPACE FLIGHTS, CLOSE-UP!
AMAZING SCIENCE BUYS
 for FUN, STUDY or PROFIT

ROTATING MULTI-COLORED LIGHT



Dazzling colors stream endlessly from constantly rotating light. Faceted, transparent globe has loured drum inside with red, green, blue & yellow stars. Bulb heat rotates drum which projects flickering star points on walls, ceilings, etc. while individual globe facets present constantly changing array of brilliant colors. 9 1/2" star—approx. 12" high on bell-shaped base. Surprisingly light. Easily placed on table. TV, fireplace—even top of Christmas tree or other display. Stock No. 71,000Q ----- \$7.00 Ppd.

JUST PRESS . . . and colors bloom!
 Liquid crystal pressure disc puts world of color under your thumb. Just press and presto—full spectrum of colors magically bloom in ever changing shapeless patterns. More pressure—deeper the color. Change viewing angle—colors change again. The secret's the amazing liquid crystals—sealed in vinyl & 3" sq. Plexiglas® disc. Look like liquid—have structure of crystal. Great conversation piece, fantastic coaster, your own portable "wet show." Stock No. 41,272Q ----- \$2.25 Ppd.

BATTERY POWERED GYROSCOPE



For the first time—have the fun & enjoyment of a gyro without bother of constant string winding & pulling. 5" diam. flying-saucer shaped. Spins on its edge, unsidedown, on your head, hanging from a string, drives rocket car, races around ring you'll be amazed at its performance. Even flipping switch to off is an experience—speeds up to a blur . . . for almost 3 min. without power. Terrific accessories incl. rocket car, pedestal. 9" diam. orbit ring, ring, pedestal, cap, chain, loop, instruct. Operates on 2 regular "C" batt. (not incl.). Stock No. 71,161Q ----- \$6.00 Ppd.

GREAT INT'L PAPER PLANE BOOK

Official fly-them-yourself book of paper airplanes from SCIENTIFIC AMERICAN'S "1st International Competition." Includes plans of all winning entries, time-of-flight records, photos, technical data, commentaries. Has 20 unusual designs on perforated pages for easy tear-out. You won't believe how some of them fly! Amusing, entertaining. 128 pages. 9" x 11 1/2". Stock No. 9391Q ----- \$2.95 Ppd.

3" ASTRONOMICAL TELESCOPE



See moon shots, orbits—stars, phases of Venus, planets close up. 60 to 180 power. Aluminized and overcoated 3" diameter f/10 primary mirror, ventilated cell. Equatorial mount with locks on both axes. Equipped with 60x eyepiece and mounted Barlow lens, 3x finder telescope, hardwood tripod. Included FREE: "STAR CHART"; 272-page "HANDBOOK OF HEAVENS"; "HOW TO USE YOUR TELESCOPE." Stock No. 85,050Q ----- \$29.95 Ppd. Stock No. 85,105Q ----- \$94.50 FOB Stock No. 85,086Q ----- \$239.50 FOB

MAIL COUPON FOR GIANT FREE CATALOG

148 Pages! More than 4,000 UNUSUAL BARGAINS!
 Enormous variety of telescopes, microscopes, binoculars, magnets, magnifiers, photo components, lenses, prisms, optical instruments, parts, Science Fair kits, projects, and accessories. Write for Free Catalog "Q" Edmund Scientific Co., 300 Edscorp Building, Barrington, New Jersey 08007.

Name _____
 Address _____
 City _____ State _____ Zip _____

EDMUND SCIENTIFIC CO. 300 EDSCORP BLDG. BARRINGTON, NEW JERSEY 08007
 ORDER BY STOCK NUMBER · SEND CHECK OR MONEY ORDER · MONEY-BACK GUARANTEE

a brand new way to say "good morning!"

The transition from the "Arms of Morpheus" to the reality of wakefulness may well be the most critical moment of your day. If waking is smooth, euphonic, punctual and civilized, everything else may well work on the same level of pleasure and efficiency. Our "Caslon 701" is the ideal transition-maker. Its unique 24-hour snooze alarm can be set for any ten-minute spot—(day or night), and isn't "alarming," but simply authoritatively insistent. It will repeat over 90 minutes, or until you mercifully shut it off! You know the exact time at a glance. Built-in glow-lamp lets you read the "701" in the pitchest dark and across king-sized rooms. 7x4x3 1/2", 110v, it comes in three decorator colors.

Send the "701" in White Avocado, or Ch. Grey (List 1st and 2nd color choice, please.) I enc. \$30.95 (\$29.95 plus \$1 for post. & ins.) Calif. add tax. Return in 2 wks. if not delighted.

Name _____
 Address _____
 Zip _____

haverhill's 584 Washington, San Francisco 94111

SNO 1003